Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

A five-day course of ivermectin may reduce the duration of COVID-19 illness

Dear Sir,

We would like to thank you for sending us the letter from Dr Ajay Kumar Shukla and Dr Saurav Misra relating to our article entitled 'A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness', published in the *International Journal of Infectious Diseases* (Ahmed et al., 2021).

This pilot study was performed to evaluate the rapidity of viral clearance and safety of a 5-day course of ivermectin or a single dose of ivermectin plus a 5-day course of doxycycline in the treatment of mild COVID-19 in adults.

The letter states that any significant antiviral activity is unlikely to be achieved by the dose used in our study and the resultant plasma concentration of the administered ivermectin. In response to the letter we would like to make few comments.

We agree with Shukla and Misra that in vitro studies have shown antiviral activities of ivermectin in plasma concentrations too high to be achieved through therapeutic doses in vivo. In this regard, firstly, we like to state that in vitro and in vivo studies of the same drug may differ in various aspects.

Viruses are known to have high rates of replication and, therefore, a one-day dose of ivermectin is unlikely to have a sufficient effect, since its half-life is around 20 hours (González Canga et al., 2008). To maintain an effective concentration of ivermectin in the body, we decided to give single ivermectin doses for 5 days.

The highest dose of ivermectin that we have used in our study is 12 mg (200 µg/kg) once daily for 5 consecutive days, which resulted in a significantly shorter time for viral clearance. Viral clearance was earlier in the 5-day ivermectin treatment arm when compared with the placebo group (9.7 days vs 12.7 days; $p = 0.02$), but this was not the case for the ivermectin + doxycycline arm (11.5 days; $p = 0.27$). Similarly, clinical trials with a 3-day, once-daily dose of 400 µg/kg oral ivermectin in dengue patients has been shown to be safe, with accelerated clearance of the dengue virus nonstructural protein 1 (Suputtamongkol et al., 2021).

In response to Shukla and Misra's comments on other retrospective studies that have shown no improvements in microbiological and virological clearance, we would like to state that a pooled analysis of six studies of ivermectin in COVID-19 patients, which included our studies, showed that ivermectin administration significantly shortened the time to negative COVID-19 RT-PCR results ($p = 0.007$) (Hariyanto et al., 2021).

Next, we like to state that ivermectin is a multifaceted medication, with antiviral as well as anti-inflamatory and anticancerous properties. Studies of ivermectin have reported potential immunomodulatory functions of the drug, which have been hypothesized to be beneficial for COVID-19 infection (Zhang et al., 2008, Ci et al., 2009, DiNicolantonio et al., 2020). We cannot rule out the effect of an immunomodulatory function of ivermectin, which could be present in vivo and play a synergistic role, including antiviral properties.

Finally, we agree with the WHO recommendation that Shukla and Misra mention in their letter. As mentioned in the 'Discussion' section, we also think that a larger randomized controlled clinical trial of ivermectin treatment is warranted to validate these important findings.

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Competing interests

None declared

Ethical approval

Not required

References

Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis 2021;103:214–16. doi:10.1016/j.ijid.2020.11.191.

González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans — a mini-review. Aaps j 2008;10(1):42–6. doi:10.1208/s12248-007-9000-9.

Suputtamongkol Y, Avirutnan P, Mairiang D, Angkasekwinai N, Niwattayakul K, Yamasmith E, et al. Ivermectin accelerates circulating nonstructural protein 1 (NS1) clearance in adult dengue patients: a combined phase 2/3 randomized double-blinded placebo controlled trial. Clin Infect Dis 2021;72(16 June 2021):e586–ee93. doi:10.1093/cid/ciaa1332.

Hariyanto TI, Halim DA, Rosalind J, Gunawan C, Kurniawan A. Ivermectin and outcomes from COVID-19 pneumonia: a systematic review and meta-analysis of randomized clinical trial studies. Rev Med Virol 2021:e2265 n/a(n/a). doi:10.1002/rmv.2265.

Zhang X, Song Y, Ci X, An N, Ju Y, Li H, et al. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflamm Res 2008;57(11):524–9. doi:10.1007/s00011-008-8007-8.

Ci X, Li H, Yu Q, Zhang X, Yu L, Chen N, et al. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. Fundam Clin Pharmacol 2009;23(4):449–55. doi:10.1111/j.1472-8206.2009.00684.x.

https://doi.org/10.1016/j.ijid.2021.07.050

DiNicolantonio JJ, Barroso J, McCarty M. Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19. Open Heart 2020;7(2). doi:10.1136/openhrt-2020-001350.

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